

Official Title: Mindfulness-Based Group Cognitive Behavior Therapy for Provoked Localized Vulvodynia

Principal Investigator: Catherine M. Leclair, MD

Professor, Department of Obstetrics and Gynecology
Oregon Health & Science University

NCT No. 02919813

Protocol Version Date: 6/19/16

Protocol

eIRB #15221 (Principal Investigator: Catherine Leclair, MD)

1. Protocol Title

Mindfulness-Based Group Cognitive Behavior Therapy for Women with Provoked Localized Vulvodynia: A Randomized Pilot Study

2. Objectives

The purpose of study is to evaluate the effectiveness of mindfulness-based group cognitive behavior therapy (M-gCBT) for the treatment of the pain and distress associated with provoked localized vulvodynia (PLV), a sexual pain condition. Women with PLV will be randomized to either M-gCBT or education only (control group) in conjunction with their usual medical care. Evaluation of pain and distress will be done through a number of measures.

3. Background

Provoked Localized Vulvodynia (PLV), previously known as *vulvar vestibulitis syndrome*, is a complex sexual pain condition affecting 8-15% of women¹⁻⁴. Women with PLV suffer from a triad of conditions that result in dyspareunia (painful intercourse): 1) localized tenderness in the vulvar vestibule (skin surrounding the vaginal opening), 2) psychosexual dysfunction, and 3) tender pelvic-floor muscles³⁻⁴. Each factor contributes significantly to deterioration in quality of life, sexual function, and psychological wellness.

With the cause of PLV unknown, a variety of treatment interventions have been explored⁴. Most studies have focused on single-modality treatments directed at the painful vestibular skin, the tender pelvic-floor muscles, or psychosexual dysfunction alone with reported improvement in pain ranging from 37-80%³⁻¹⁸. Psychosexual counseling is an important but often neglected component of care. Women with PLV report higher rates of sexual dysfunction with poor arousal, low desire, and impaired orgasm¹⁹⁻²³. Co-morbidities of mood disturbances, anxiety, depression and relationship disruption have been identified in most women with PLV²⁰⁻²⁷. Chronic dyspareunia results in anticipatory anxiety²⁸ (fearing sexual encounters before they occur) and leads to avoidant feelings about sex. Although sexual therapy and cognitive-based counseling are routinely recommended to women with PLV, many affected women are reluctant to seek psychosexual counseling services for a number of reasons. These include unavailability of services, the stigma associated with one-on-one sex therapy, and insurance limitations.

Group Cognitive Behavioral Therapy (gCBT) is a type of psychological counseling that aims to reduce anxiety, fear, and avoidance associated with dyspareunia by teaching women to have more control over their pain through cognition and education. gCBT has been studied in women with PLV^{6,11-12, 16-18,28} and shown to be effective in reducing the pain and distress associated with this condition. Weijmar¹⁷ found that 80% of his subjects benefited from CBT, even in a subgroup that pursued other treatments for PLV. Abramov¹² found that, in a cohort of patients whose pain was not resolved with vestibulectomy and pelvic-floor physical therapy (PT), sexual counseling was the final treatment that enabled them to resume full sexual activity without pain. In a prospective study¹¹, 76 women who completed gCBT reported less intercourse pain and sexual dissatisfaction, compared to pre-treatment scores. In a RCT by Bergeron¹⁸ comparing single modality treatments (gCBT vs. pelvic-floor PT vs.

vestibulectomy), all three groups improved, however none greater than 52%. This evidence suggests that single modality therapies do not manage all facets of pain for most women with PLV.

Mindfulness-gCBT (M-gCBT) is a technique that combines meditation with elements of gCBT²⁸. Traditional CBT methods stress education and knowledge, therefore improving coping through cognition. Mindfulness is a strategy of becoming aware of incoming thoughts and feelings and learning to accept rather than react or attach to them. Combined M-gCBT changes the automatic process of recognizing distressful stimuli (e.g. pain, distress) to observing and accepting these stimuli without judgment.

While Mindfulness was initially developed as a treatment technique for depression³⁰⁻³² it has successfully been extrapolated for use in anxiety and chronic pain³⁰⁻³⁵. The practice of Brief Body Scanning, a mindfulness technique, has been shown to result in a significantly greater reduction in both experimentally-induced and chronic pain than exposure to an informational video³⁴⁻³⁵. Basson proposed a model which reflects how stress-induced changes of pain amplification (central sensitization) exacerbate the sexual dysfunction precipitated by the pain of intercourse³⁶. Mindfulness-based CBT was suggested as a promising approach to target both the pain and sexual distress of PVD. In one study reviewing the relationship of stress, chronic pain and sexual response in women with PLV, women participating in a multidisciplinary vulvodynia program that included Mindfulness-gCBT were found to have significantly less dyspareunia and sex-related distress.³⁷ However, a major weakness of this study was the absence of a control group.

Since M-gCBT teaches patients to identify destructive behaviors such as ruminative thoughts with nonjudgmental observation³⁶⁻⁴¹, we hypothesize that it would be a useful technique to treat the underlying psychosexual distress in patients with PLV. The group format is thought to provide several therapeutic benefits, including mutual support, increased compliance and decreased isolation^{6,37,42-44}. M-gCBT also emphasizes home practice (e.g. Body Scanning) as reinforcement of the group sessions. Thus, M-gCBT offers a hopeful strategy to manage the complex psychosexual distress associated with PLV.

While M-gCBT appears to be a promising approach for treatment of PLV, the intensive nature of the program and time commitment represent potential barriers to acceptability. While recruitment and treatment credibility were problems in the Bergeron et al RCT evaluating a 12 session gCBT program, none of the 28 subjects randomized to this group dropped out once the sessions were begun.¹⁸ However, a condensed M-gCBT skill development approach has also been shown to be effective in decreasing anticipatory pain³⁴⁻³⁵. One study evaluating the effects of Body Scanning on pain and anxiety showed that 20min/day practiced daily for 3 days reduced pain.³⁴ This suggests that Mindfulness techniques may be beneficial even after short intensive training.

Inconvenience of time, complexity of treatment, distance to care site, location and cost all influence the initiation and adherence to any therapeutic service⁴². Participation in a group has been shown to be more successful at increasing patient adherence to treatment than education alone^{6,42}. We hypothesize that a shorter more focused M-gCBT program may be just as effective as longer therapies, while also being less expensive and more acceptable to women. An 8 week program introduced at the University of British Columbia Multidisciplinary Vulvodynia Program showed promise in reducing pain and sex-related distress associated with PLV³⁷. We propose a randomized trial to validate this approach.

4. Study Design

An initial pilot will be conducted to determine feasibility and acceptability of care. Since inconvenience of time, adherence to an 8-week program and complexity of treatment are all factors that may deter enrollment, a pilot will offer valuable information. This pilot cohort will include 6-12 women with PVD. This cohort will participate in the mindfulness-group cognitive behavior therapy (one arm of the RCT) and participate in all outcome measures. Following this initial pilot (and potential modification of the protocol), screening and enrollment will occur for the randomized clinical trial.

This is a randomized controlled pilot study that will evaluate introital pain and psychosexual function before and after treatment in an 8 week program of either M-gCBT or education alone (control group). Vaginal insertion pain (Tampon Test) is the primary outcome. Sexual function and quality of life will also be evaluated.

5. Study Population

a. Number of Subjects

The total number of subjects we expect to complete the study (two-three cohorts over 12 months; 1 cohort/2 groups/6-12 subject per group) is 24-48 subjects and we expect to have a total of 60 subjects over the entire year enrolled into the study to account for screen failures.

b. Inclusion and Exclusion Criteria

Subjects will be recruited through the PVH (Program in Vulvar Health), word of mouth or by advertisements.

Inclusion Criteria:

- a. Reported dyspareunia for at least 6 months in non-pregnant, healthy women aged 18-55 years old meeting Friedrich's criteria for PLV.⁵¹
- b. Qtip Test^{51-52, 54} mean verbal rating score of $\geq 4/10$ in 4 of 6 defined points of the vestibule (2, 4, 6, 8, 10, 12 o'clock), and have received a Qtip Test score of verbal $\leq 2/10$ for the labia majora and minora, intra labial sulcus, and perineum.
- c. Ability to insert a regular Tampax® tampon.
- d. Baseline tampon test pain score ≥ 80 mm.
- e. Phone access.
- f. Lives within 60 miles with reliable transportation.

Exclusion Criteria:

- a. Pregnancy.
- b. Active counseling or mindfulness training (within 6 months of study).
- c. Any other clinical reason for dyspareunia (endometriosis pain, chronic pelvic pain, vulvar dermatoses such as psoriasis, lichen sclerosus, etc).
- d. Impaired cognition or disruptive behavior not conducive to group dynamic.
- e. Planned long term travel or surgery during study period.
- f. Unable or unwilling to complete baseline assessments or agree to be randomized.
- g. Axis 2 diagnosis, chronic substance abuse, suicidality or disruptive to group dynamic.
- h. Non-English speaking.

c. Vulnerable Populations

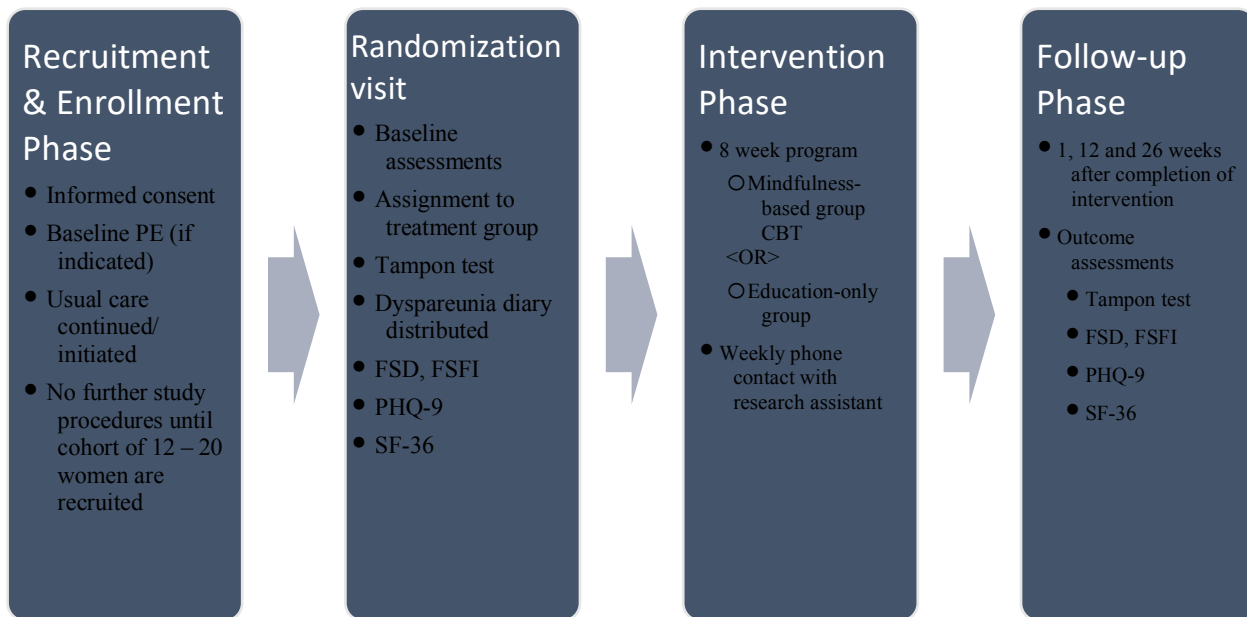
Children, pregnant women, neonates, decisional impaired, and prisoners will be excluded from the study.

d. Setting

Over 400 new and 800 return patients are seen annually in the Program in Vulvar Health (PVH), an OHSU specialty referral clinic serving the Pacific NW. Between 2009-2011, 43% of new patients were diagnosed with PLV. The PVH offers comprehensive care for women with PLV. However, psychosexual counseling is currently offered only in a traditional one-on-one setting within our center or in the community. Resources for sexual counseling, particularly how it pertains to sexual pain, are limited. Most women with PLV do not receive treatment of the psychosexual component of this pain triad.

e. Recruitment Methods

We will recruit subjects from our clinic population and use advertisement if necessary. Clinic patients with PLV will receive information about the study at the time of her appointment in the Program in Vulvar Health. Women who inquire through advertisements will be screened by the study coordinator and evaluated by the PI (history and physical exam). After informed consent procedures, those who meet all eligibility and no exclusion criteria will be offered enrollment. A consenting subject will be informed that it may take several weeks to assemble the group, and that she will be contacted when sessions will begin (anticipate up to 8 weeks). Once an adequate number (12-24/cohort) of participants is reached, subjects will be contacted by telephone to gauge ongoing interest. Those that wish to continue with the study will have inclusion/exclusion criteria reviewed and will be randomized to attend the M-gCBT or education-only (control) group sessions. Since previous research shows that a minimum number of 6 but a maximum number of 12 is effective for group therapy, the goal will be to enroll 12 in each arm, but will be balanced to reduce wait time for subjects interested in starting groups to no more than 8 weeks. After enrollment, randomization will occur. The study team (a staff member of the Women's Health Research Unit not directly involved in the conduct of the study) will prepare group assignments using a computer-generated, random numbered list. The group allocation will be concealed in consecutively numbered opaque envelopes. The research assistant will select the next consecutive number for each enrolled subject. After randomization, all subjects will be followed according to intention to treat.



f. Consent Process

The consent process will be done in the Center for Women’s Health (CWH) at OHSU either during a clinic appointment or at another time at the subject’s convenience (either in the CWH or the Women’s Health Research Unit). The consent process will be done by the PI and/or research assistant (RA) who will review the consent form in its entirety with the subject and review the purpose, procedure, risks, and benefits with the subject. Only subjects that have been consented will be enrolled in the study.

6. Procedures Involved

The study participation will consist of three separate phases: 1) Recruitment and Enrollment (1-12 weeks); 2) Intervention (8 weeks); and Follow-up (26 weeks). Subjects will continue to receive usual care for their PLV, but will agree not to undergo surgery during the first 2 phases (potential for missed group sessions). During the Recruitment phase, subjects will undergo screening, informed consent and enrollment. After Enrollment, subjects may continue usual care for PLV. Once a complete cohort has been assembled (minimum of 12 subjects/1 cohort/2 groups), subjects will be contacted for participation in the Intervention phase by a RA from The Women’s Health Research Unit (WHRU) who will arrange a time to review and complete the questionnaires, the Dyspareunia Diary, and Tampon Test. Randomization will occur at this visit. During the 8 week Intervention phase, each participant will attend the assigned group session, and complete a subject diary. Women in the M-gCBT group will attend weekly 2 hour sessions at the Center for Women’s Health (same location as Program in Vulvar Health). Control women will attend 8 weekly group education seminars in the Center for Women’s Health. These sessions will include an informational video clip reviewing some aspect of PLV and sexuality followed by an unstructured group discussion facilitated by an instructor. The video clips will be “chapters” taken from the educational video “Exploring Women’s Sexuality” and “Vestibulodynia: A Common Cause for Painful Intercourse”. (Accessible through OHSU Box Account <https://ohsu.box.com/s/ldjx8pl3kwc6qcgtnw00b8w9qqn1tcr>). Outcome questionnaires and pain assessments will be completed one, 12 and 26 weeks after the last group session (when possible, they will occur at the same time as the patient’s next regular clinic visit). Otherwise, follow-up questionnaires and pain assessments will be collected via email or regular mail. If a subject withdraws from the research, their

data up to the point of withdrawal will be included in the data analysis, but no ongoing data collection will occur beyond the point of withdrawal.

7. Data and Specimens

a. Handling of Data and Specimens

Information included in the data will be demographics including age, race, type of PLV, duration of PLV, medication list, , dyspareunia diary, results of the tampon test, patient questionnaires. Electronic data will be stored on restricted drives on the OHSU network. Paper files (including questionnaires and daily diary forms) will be stored in locked filing cabinets in restricted access offices at OHSU.

b. Sharing of Results with Subjects

Study results will be shared with subjects at the conclusion of the study.

c. Data and Specimen Banking

The data will be used as pilot data to help guide the development of future research projects (R01) that incorporate M-gCBT into an evaluation of medical and surgical therapy, and assess long term results with these therapies. The data does not include genetic research.

De-identified data will be stored in the Women's Health Research Unit Repository (IRB # 6748) for future research purposes. Data will be stored on a secure server at OHSU with access limited to the PI and approved study team members. All repository submittal and release procedures will be managed by the Guardian of the WHRU Repository and follow all guidelines as outlined in the protocol.

8. Data Analysis

The primary outcome of this study will be the Tampon Test. Developed by Foster, et al⁵⁴, this test is a validated tool that measures introital pain with PLV by having the woman insert and remove a standard tampon (Tampax Original Regular™) and then score pain on a 100-mm VAS⁵⁵⁻⁵⁹. The test is a reliable correlate to intercourse pain and the QtipTest⁵¹⁻⁵². The Tampon Test is an alternative to intercourse that subjects can almost always perform (in one study, 96.3%⁵⁴).

The primary outcome will be the reduction in pain measured by the Tampon Test tested one week after the intervention phase. We assume a baseline Tampon Test pain (VAS) of 80 mm (SD 14 mm) based on our preliminary data and the work of others^{14,53-54}, and expect that the mean reduction in pain will be 20 mm in the control group and 40 mm in the M-gCBT group. To detect a mean difference of 20mm, a sample size of 10 per cohort is required. We plan to enroll 12 women per cohort (2 cohorts over 12 months) in order to allow a 20% drop out rate prior to randomization. A mean difference of 20 mm correlates with the range of minimal to moderate changes in pain in clinical trial outcome measures⁵⁵⁻⁵⁹.

Important psychosexual secondary outcomes will be evaluated via questionnaires measuring sexual function, depression and quality-of-life (QOL). These results will provide preliminary data for a future R01 application. The Female Sexual Distress Scale (FSD) is a validated, 12-item scale that evaluates a woman's subjective distress associated with sexual dysfunction⁶⁰⁻⁶² that is sensitive to the effects of treatment. The Female Sexual Function Index (FSFI) is a widely accepted, validated survey tool to evaluate sexual dysfunction including pain.^{60, 63-66} The Pain Catastrophizing Scale is a 13 item validated questionnaire measuring the magnification, rumination and helplessness women experience with the threat of painful stimuli⁷⁰. Women with PLV also have higher rates of depression and anxiety.²⁰⁻²⁷ The

Beck Depression Inventory (BDI-PC) and General Anxiety Disorder-7 (GAD-7) are well-validated tool that measure the current state of depression and/or anxiety and are commonly used in the clinical and research setting⁶⁸⁻⁶⁹.

Validated subject written educational materials (for the Dyspareunia Diary and Tampon Test) used in a large RCT (NIH NCT01301001) have been obtained (with permission). Subjects will record introital pain intensity weekly with the Tampon Test using 100-mm VAS. The RA will phone each subject weekly to review information in the diary. The weekly call will also serve as a reminder for subjects to stay engaged in all data-collection efforts. Finally, other important outcomes such as patient satisfaction and revenue outcomes (cost to conduct program) will be measured.

9. Privacy, Confidentiality, and Data Security

Standard institutional practices will be followed as described in the OHSU Information Security and Research Data Resource Guide (http://ozone.ohsu.edu/cc/sec/isg/res_sec.pdf) to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures. Paper files will be stored in locked filing cabinets in restricted access offices at OHSU. Electronic data is stored on restricted drives on the OHSU network. Access to data/specimens is restricted to study personnel. Access to data requires OHSU ID/password authentication. Upon enrollment, subjects will be assigned a code that will be used instead of their name, medical record number or other personally identifying information. Electronic files for data analysis will contain only the subject code.

Codes will not contain any part of the 18 HIPAA identifiers (initials, DOB, MRN) The key associating the codes and the subjects personally identifying information will be restricted to the PI and study staff. The key will be kept secure on a restricted OHSU network drive a in a limited access folder. De-identified data will be stored in the Women's Health Research Unit Repository (IRB #6748) at the completion of this study and will be released for future uses per the repository protocol.

10. Provisions to Monitor the Data to Ensure the Safety of Subjects

The investigators and study staff are responsible for recording the data, and they will be verifying its accuracy throughout the process. Dr. Leclair, the PI, will be reviewing the data in-depth periodically throughout the study. The PI will also be overseeing that the study procedures are being carried out as per the approved protocol via close supervision of the study visit and procedures and through frequent communication with the other investigators and staff. Anytime that an AE, SAE, UP or protocol deviation is reported by an investigator or study staff, the PI will review and assess the data, and proceed as per OHSU reporting policy. Otherwise, the PI entity will be reviewing the records periodically throughout the study. All adverse events will be assessed and reportable UPs will be submitted to the IRB, if judged related to the study protocol.

11. Risks and Benefits

a. Risks to Subjects

Possible risks of the study include a low risk of breach of confidentiality, time commitment of subjects to the group sessions, transportation needed to participate in group sessions, and increased anxiety or psychological distress potentially generated during groups discussions, particularly when discussing

intimate subjects. Our aim is that the potentially increased anxiety at time of discussions will ultimately be lessened through the intervention.

b. Potential Benefits to Subjects

Potential benefits include decrease in dyspareunia and psychosexual distress along with the generation of a sense of community among subjects with PLV that participate in this group therapy.